Rejection of Claims 18, 20-37 and 60-65 Under 35 U.S.C. §112, First Paragraph

Claims 18, 20-37 and 60-65 stand rejected under 35 U.S.C. §112, first paragraph, on the grounds that these claims contain subject matter which is not described in the specification in such a way as to enable one skilled in the art to practice the invention. Applicants again respectfully traverse these rejections.

As in the previous Office Action and Applicants' previous Response, there are six general points at issue, and Applicants wish to respond point by point:

1. The Office Action objects that "the claims recite no 'specific' receptor to be inhibited, nor do they recite structurally defined components to practice the instant invention, in which each G-protein receptor dysfunction characterizes its own unique disease state . . . Therefore, the claims fail to specify how the skilled artisan knows when they have successfully practiced the instant invention, without requiring undue experimentation to discover how to make and use Applicants' invention."

First, Applicants note that claims 25-27 (D1 dopamine receptor), 30-31 (β1-adrenergic receptor), and 33-34 (α1A-adrenergic receptor), as well as the claims which are dependent on these claims, do in fact recite a "specific receptor" to be inhibited and do, in fact, recite "structurally defined components" in the form of amino acid sequences. Furthermore, claims 28, 32, and 35 further limit these claims by reciting the specific disorders which are treated. Applicants respectfully submit that it is well known in the art how to synthesize and administer specific polypeptides, as well as how to determine when these receptors are being inhibited, or these disorders are being beneficially treated. Therefore, Applicants respectfully submit that, at least with respect to these claims, the subject matter is fully enabled and the rejection should be withdrawn.

Moreover, as embodied in these claims, the specification discloses examples of methods relating to a multiplicity of different integral membrane proteins (e.g., G protein coupled receptors such as dopamine receptors, adrenergic receptors, etc.), and a multiplicity of different

antagonist peptides (e.g., the peptides recited in claims 25-27, 30-31, and 33-34), which can be used to treat a multiplicity of different disorders for which administration of an antagonist is indicated (e.g., the disorders recited in claims 28, 32, and 35). Each of these examples, however, relates to more general methods which are enabled by the specification. Therefore, in light of the disclosure of these multiple examples or species, Applicants respectfully submit that the specification enables the broader claims, reciting for example the genus of integral membrane proteins (e.g., claim 18) or the genus of G-protein coupled receptors (e.g., claim 22), or reciting that the antagonist peptide consists essentially of at least four consecutive amino acid residues from at least one transmembrane domain of the integral membrane protein (or a conservative substitution variant thereof), or reciting generally that the disorder is one for which administration of an antagonist of the integral membrane protein is indicated. Thus, Applicants respectfully submit that the rejections under 35 U.S.C. §112, first paragraph, based on these considerations should be withdrawn.

2. The Office Action objects, with respect to claims 18, 21-23, 29-30, and 33, that the "specification is clearly deficient in providing sufficient guidance for knowing how to effect measurable phenotype as it relates to generic adrenergic receptors, as currently claimed, without requiring undue experimentation." Again, Applicants must respectfully disagree. The methods of the invention are to used to treat disorders for which administration of an integral membrane protein is indicated. Such disorders are known in the art, and include those which are specifically disclosed in the specification. For each such disorder, the integral membrane protein must, by definition, be known in order for administration of an antagonist to be indicated. For each such integral membrane protein, the transmembrane domains will either be known, or may be easily determined without undue experimentation. For adrenergic receptors, there are methods, known in the art, for measuring inhibition of receptor activity (i.e., effecting measurable phenotype) either directly or indirectly. Thus, with respect to any given adrenergic receptor, and in light of the teachings of the specification, Applicants respectfully submit that one of ordinary skill in the art is enabled to choose an antagonist peptide consisting essentially of at

least four consecutive amino acid residues from a transmembrane domain of that adrenergic receptor (or a conservative substitution variant thereof), and to administer that peptide to treat a disorder for which administration of an antagonist of that adrenergic receptor is indicated. Moreover, the specification provides several examples of the practice of such methods. Thus, Applicants respectfully submit that the rejections under 35 U.S.C. §112, first paragraph, based on these considerations should be withdrawn.

3. The Office Action objects that the claims do not "recite what structurally constitutes 'an antagonist...', nor what disorder or symptom is to be treated, each with their own unique etiology, nor when the skilled artisan knows when, where or what 'is indicated', because no such recitation is claimed so that the skilled artisan knows when they are in possession of the necessary components to practice the instant invention; thereby, requiring undue experimentation." Applicants are uncertain as to the meaning of this passage.

The term "antagonist" describes a molecule with a particular functional characteristic: It inhibits, opposes, or impedes the activity or functioning of some reference molecule. Thus, for example, an adrenergic receptor antagonist inhibits the activity of an adrenergic receptor. The structure of antagonists undoubtedly determines their ability to function as antagonists, but the term "antagonist" is to be understood functionally. Therefore, it is not clear why the Office Action objects that the claims do not "recite structurally what constitutes 'an antagonist'." With respect to the practice of the methods of the invention, it may be practiced whenever administration of an antagonist, understood functionally, is indicated. With respect to the antagonist peptides of the invention, they are indeed defined structurally, as consisting essentially of at least four consecutive amino acid residues from a transmembrane domain of the relevant integral membrane protein (or a ~~conservative substitution~~ variant thereof).

With respect to what disorders or symptoms are to be treated, and what "is indicated", Applicants note that the term "indication," and the phrase "is indicated," have special meanings in the medical arts. For example, an "indication" is defined as the "basis for initiation of a treatment for a disease or of a diagnostic test [which] may be furnished by a knowledge of the

cause ..., by the symptoms present ..., or by the nature of the disease ..." (*Stedman's Medical Dictionary*, 26th Edition, Williams Wilkins, Baltimore, MD, 1995). Thus, administration of an antagonist of an integral membrane protein *is indicated* whenever there is basis for initiating treatment with such an antagonist. Such indications are well known in the art. Merely as an example, the entry for the β-adrenergic blocking agent (i.e., antagonist) COREG® in the *Physician's Desk Reference*, 53rd Edition, Medical Economics Company, Inc., Montvale, NJ, 1999 (copy attached), states under the heading "INDICATIONS AND USAGE" and subheading "Hypertension" that "Coreg (carvediol) is also indicated for the management of essential hypertension." *The Physician's Desk Reference* and the medical literature are teeming with such examples.

Therefore, Applicants respectfully submit that one of ordinary skill in the art will clearly know when administration of an antagonist of any given integral membrane protein is indicated, and will, in light of Applicants disclosure, be enabled to administer an antagonist peptide consisting essentially of at least four consecutive amino acid residues from a transmembrane domain of that protein (or a conservative substitution variant thereof). Thus, Applicants respectfully submit that the rejections under 35 U.S.C. §112, first paragraph, based on these considerations should be withdrawn.

4. The Office Action objects that "nowhere in the claims is there any recitation to indicate when such administration [of an antagonist of an EGF receptor to treat a neoplastic growth] 'is not indicated'; thereby encompassing all neoplastic growths . . . [that] the claims do not recite using any specific peptide to specifically 'inhibit growth' of any tumor" and that undue experimentation would be required to practice the invention. As noted above, the medical literature is full of examples of indications for administering antagonists of various integral membrane proteins, including EGF receptors. With respect to reciting specific peptides, the claims recite that the peptide consists essentially of at least four consecutive amino acid residues from a transmembrane domain of the relevant integral membrane protein (or a conservative

substitution variant thereof). With respect to the comments relating to neoplastic growths and the inhibition of tumor growth, Applicants note again that the methods may be practiced to treat neoplastic growths for which administration of an EGF receptor antagonist is indicated, and that one of ordinary skill in the art can identify such indications without undue experimentation. Thus, Applicants respectfully submit that the rejections under 35 U.S.C. §112, first paragraph, based on these considerations should be withdrawn.

5. The Office Action objects that "the specification still provides contradictory evidence [relating to GABA receptors] on how to determine how and when to successfully practice the invention, without requiring undue experimentation [and that] the claims do not recite using any specific peptide to specifically 'inhibit GABA receptors' that effects any measurable phenotype." Again, the claimed invention is to be practiced whenever administration of an integral membrane protein antagonist is indicated, and such indications, including indications for the administration of GABA receptor agonists, are known in the art. Further, as before, the specific antagonist peptides are those which consist essentially of at least four consecutive amino acid residues from a transmembrane domain of the relevant integral membrane protein (or a conservative substitution variant thereof). Thus, Applicants respectfully submit that the rejections under 35 U.S.C. §112, first paragraph, based on these considerations should be withdrawn.

6. The Office Action objects that claims "the claims still fail to recite using any specific peptide to specifically 'inhibit dopamine and/or monoamine transporters' that effect any measurable cell type, disease state, or measurable phenotype" and therefore are not enabled. Again, Applicants point out that the specific peptides to inhibit any such transporter consist essentially of at least four consecutive amino acid residues from a transmembrane domain of the relevant transporter (or a conservative substitution variant thereof), and that methods of measuring the inhibition of such transporters are well known in the art. Thus, Applicants respectfully submit that the rejections under 35 U.S.C. §112, first paragraph, based on these considerations should be withdrawn.

Rejection of Claims 18-20, 27, and 36 Under 35 U.S.C. §112, Second Paragraph

Claims 18, 20-37 and 60-65 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite for reciting the phrases "administration of an antagonist . . . is indicated" and "consisting essentially of at least four consecutive residues".

The meaning of the phrase "is indicated" has been discussed extensively above. Applicants respectfully submit that the phrase is not indefinite and that its wide usage in the medical literature is indicative of the fact that one of ordinary skill in the art would understand its meaning. Thus, Applicants respectfully submit that the rejections under 35 U.S.C. §112, second paragraph, based on these considerations should be withdrawn.

With respect to the phrase "consisting essentially of at least four consecutive amino acid residues," Applicants draw the Examiner's attention to, for example, U.S. Pat. No. 5,298,599 (claim 5), U.S. Pat. No. 5,229,491 (claim 1), U.S. Pat. No. 5,229,286 (claim 1), U.S. Pat. No. 5,319,071 (claim 2), and U.S. Pat. No. 5,494,672 (claim 1). Each of these patents has claims drawn to peptides "consisting essentially of" some reference amino acid sequence, and provides evidence that this term has acquired a definite meaning within U.S. patent practice as it relates to claims involving polypeptides. In the present case, the reference sequence is any sequence of at least four consecutive amino acids from a transmembrane domain of the relevant integral membrane protein (or a conservative substitution variant thereof). A peptide which consists of fewer than four amino acid residues could not meet this definition. However, a peptide which consists in essence of four consecutive residues from such a transmembrane domain, but which includes additional residues at the N- and/or C-terminus which do not alter the essential function ~~of the peptide in the context of the invention, would fall within the scope of the definition. Thus,~~ in light of the accepted use of such claim language, Applicants respectfully submit that the rejections under 35 U.S.C. §112, second paragraph, based on these considerations should be withdrawn.

SUMMARY

Claims 18, 20-37 and 60-65are pending in the application and remain under consideration. No amendments to the claims are made herein. A petition for a two-month extension of time for response, up to and including September 28, 1999, and an authorization to charge the necessary fee to Deposit Account No. 20-0531, are transmitted herewith. Applicants believe that no other fees are due at this time. In the event that additional fees are due, the Commissioner is hereby authorized to charge such fees to said account.

Applicants request that the Examiner reconsider the application in light of the foregoing remarks. If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

Respectfully submitted,

Date: September 28, 1999
Reg. No. 38,349

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[illegible] Dosage: More than 1 day's therapy is sel- [illegible]

	Usual Dosage	Not to Exceed
[illegible]	not recommended	
[illegible]	2½ mg 1 or 2 times a day	7.5 mg per day
[illegible]	2½ mg 2 or 3 times a day	10 mg per day
[illegible]	2½ mg 3 times a day or 5 mg 2 times a day	15 mg per day

[illegible] Calculate each dose on the basis of 0.06 mg of [illegible] lb of body weight; give by deep I.M. injection. [illegible] ally obtained with one dose.

[illegible] Children:

[illegible] Dosage: For children 2 to 12 years, starting [illegible] mg 2 or 3 times daily. Do not give more than [illegible] first day. Then increase dosage according to pa- [illegible] nse.

[illegible] 2 to 5, total daily dosage usually does not exceed [illegible]

[illegible] 6 to 12, total daily dosage usually does not ex- [illegible]

[illegible] For ages under 12, calculate each dose on the [illegible] mg of Compazine (prochlorperazine) per lb of [illegible] give by deep I.M. injection. Control is usually [illegible] one dose. After control is achieved, switch the [illegible] oral form of the drug at the same dosage level [illegible]

[illegible] AGE

[illegible] VERSE REACTIONS.)

[illegible] Primarily involvement of the extrapyrami- [illegible] producing some of the dystonic reactions de- [illegible] central nervous system depression to the point [illegible] or coma. Agitation and restlessness may also [illegible] possible manifestations include convulsions, [illegible] and cardiac arrhythmias, fever and auto- [illegible] such as hypotension, dry mouth and ileus.

[illegible] It is important to determine other medica- [illegible] by the patient since multiple-dose therapy is [illegible] overdosage situations. Treatment is essentially [illegible] and supportive. Early gastric lavage is helpful. [illegible] under observation and maintain an open air- [illegible] involvement of the extrapyramidal mechanism [illegible] dysphagia and respiratory difficulty in severe [illegible] **Do not attempt to induce emesis because a [illegible] action of the head or neck may develop that [illegible] in aspiration of vomitus.** Extrapyramidal [illegible] may be treated with anti-parkinsonism drugs, [illegible] or *Benadryl*. See prescribing information for [illegible] Care should be taken to avoid increasing [illegible] depression.

[illegible] ation of a stimulant is desirable, amphetamine, [illegible] etamine or caffeine with sodium benzoate is rec- [illegible]

[illegible] that may cause convulsions (e.g., picrotoxin or [illegible] ezol) should be avoided.

[illegible] on occurs, the standard measures for managing [illegible] hock should be initiated. If it is desirable to ad- [illegible] vasoconstrictor, *Levophed* and *Neo-Synephrine* [illegible] table. Other pressor agents, including epineph- [illegible] recommended because phenothiazine deriva- [illegible] verse the usual elevating action of these agents [illegible] further lowering of blood pressure.

[illegible] rience indicates that phenothiazines are *not* di- [illegible]

[illegible] on, Spansule, *capsules* —Since much of the [illegible] psule medication is coated for gradual release, [illegible] ected at reversing the effects of the ingested [illegible] supporting the patient should be continued for [illegible] overdosage symptoms remain. Saline cathartics [illegible] in hastening evacuation of pellets that have not [illegible] sed medication.

[illegible] PLIED

[illegible] and 10 mg, in bottles of 100; in Single Unit Pack- [illegible] intended for institutional use only): [illegible]

[illegible] NDC 0007-3366-20

[illegible] 's: NDC 0007-3366-21

[illegible] NDC 0007-3367-20

[illegible] 100's: NDC 0007-3367-21

[illegible] ides—10 and 15 mg, in bottles of 50:

[illegible] NDC 0007-3344-15

[illegible] NDC 0007-3346-15

[illegible] mg/mL), in boxes of 25 and 10 mL (5 mg/mL), [illegible]

[illegible] in boxes of 25: NDC 0007-3352-16 [illegible]

[illegible] mL), in boxes of 1: NDC 0007-3343-01 [illegible]

Suppo[illegible]—$2^1/_2$ mg (for young children), 5 mg (for older children) [illegible] 25 mg (for adults), in boxes of 12:

$2^1/_2$ mg, in boxes of 12: NDC 0007-3360-03

5 mg, in boxes of 12: NDC 0007-3361-03

25 mg, in boxes of 12: NDC 0007-3362-03

Syrup—5 mg/5 mL (1 teaspoonful) in 4 fl oz bottles:

5 mg/5 mL, 4 fl oz: NDC 0007-3363-44

Store Compazine (prochlorperazine) vials below 30°C (86°F). Do not freeze. Other dosage forms can be stored between 15° and 30°C (59° and 86°F). Protect from light.

* norepinephrine bitartrate, Sanofi Winthrop Pharmaceuticals.

† phenylephrine hydrochloride, Sanofi Winthrop Pharmaceuticals.

‡ phenytoin, Parke-Davis.

§ metrizamide, Sanofi Winthrop Pharmaceuticals.

‖ diphenhydramine hydrochloride, Parke-Davis.

Veterans Administration/Military/PHS—Vials, 2 mL, 25's, 6505-01-230-3931; 10 mL, 1's, 6505-00-684-9630; Suppositories, $2^1/_2$ mg, 12's, 6505-00-133-5213; 5 mg, 12's, 6505-01-153-2894; 25 mg, 12's, 6505-00-133-5214; Syrup, 5 mg/5 mL, 4 fl oz, 6505-01-039-6849; Tablets, 5 mg, 100's, 6505-00-761-5640; 5 mg, 100's (SUP), 6505-00-118-2563; 10 mg, 100's, 6505-01-354-1042; 10 mg, 100's (SUP), 6505-00-092-3189.

CZ:L90

Shown in Product Identification Guide, page 339

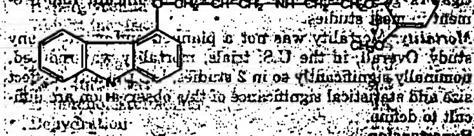
COREG® ℞

[*kō-reg*]

brand of carvedilol Tablets

DESCRIPTION

Carvedilol is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. It is a racemic mixture with the following structure:



carvedilol

Tablets for Oral Administration

Coreg (carvedilol) is a white, oval, film-coated tablet containing 3.125 mg, 6.25 mg, 12.5 mg or 25 mg of carvedilol. The 6.25 mg, 12.5 mg and 25 mg tablets are Tiltab® tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose and titanium dioxide.

Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1) and intestinal fluid (simulated, TS without pancreatin, pH 7.5).

CLINICAL PHARMACOLOGY

Coreg is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. *Coreg* has no intrinsic sympathomimetic activity.

Pharmacokinetics

Coreg is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking *Coreg* with food should minimize the risk of orthostatic hypotension.

Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted p[illegible]ly via the bile into the feces. Demethylation and hydro[illegible]n at the phenol ring produce three active metabolites [illegible] β-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade. Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol.

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S-mephenytoin (patients deficient in cytochrome P450 2C19).

Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L, indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to 700 mL/min.

Congestive Heart Failure: Steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally over the 6.25 to 50 mg dose range in patients with congestive heart failure. Compared to healthy subjects, congestive heart failure patients had increased mean AUC and C_{max} values for carvedilol and its enantiomers, with up to 50% to 100% higher values observed in 6 patients with NYHA class IV heart failure. The mean apparent terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

Pharmacokinetic Drug-Drug Interactions: Since carvedilol undergoes substantial oxidative metabolism, the metabolism and pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450 enzymes.

Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70%.

Cimetidine: In a pharmacokinetic study conducted in 10 healthy male subjects, cimetidine (1000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change in C_{max}.

Glyburide: In 12 healthy subjects, combined administration of carvedilol (25 mg once daily) and a single dose of glyburide did not result in a clinically relevant pharmacokinetic interaction for either compound.

Hydrochlorothiazide: A single oral dose of carvedilol 25 mg did not alter the pharmacokinetics of a single oral dose of hydrochlorothiazide 25 mg in 12 patients with hypertension. Likewise, hydrochlorothiazide had no effect on the pharmacokinetics of carvedilol.

Digoxin: Following concomitant administration of carvedilol (25 mg once daily) and digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were increased by 14% and 16%, respectively, in 12 hypertensive patients.

Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant differences in their pharmacokinetics compared with administration of the drugs alone.

Warfarin: Carvedilol (12.5 mg twice daily) did not have an effect on the steady-state prothrombin time ratios and did not alter the pharmacokinetics of R(+)- and S(-)-warfarin following concomitant administration with warfarin in 9 healthy volunteers.

Continued on next page

Information on the SmithKline Beecham Pharmaceuticals products appearing here is based on the labeling in effect on July 31, 1998. Further information on these and other products may be obtained from the Medical Department, SmithKline Beecham Pharmaceuticals, One Franklin Plaza, Philadelphia, PA 19101.

Special Populations

Elderly: Plasma levels of carvedilol average about 50% higher in the elderly compared to young subjects.

Hepatic Impairment: Compared to healthy subjects, patients with cirrhotic liver disease exhibit significantly higher concentrations of carvedilol (approximately 4- to 7-fold) following single-dose therapy (see WARNINGS, Hepatic Injury).

Renal Insufficiency: Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment. Based on mean AUC data, approximately 40% to 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function. However, the ranges of AUC values were similar for both groups. Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in patients with impaired renal function.

Consistent with its high degree of plasma protein-binding, carvedilol does not appear to be cleared significantly by hemodialysis.

Pharmacodynamics and Clinical Trials

Congestive Heart Failure

Pharmacodynamics

The basis for the beneficial effects of Coreg (carvedilol) in congestive heart failure is not established.

Two placebo-controlled studies compared the acute hemodynamic effects of *Coreg* to baseline measurements in 59 and 49 patients with NYHA class II-IV heart failure receiving diuretics, ACE inhibitors, and digitalis. There were significant reductions in systemic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate. Initial effects on cardiac output, stroke volume index, and systemic vascular resistance were small and variable.

These studies measured hemodynamic effects again at 12 to 14 weeks. *Coreg* significantly reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic vascular resistance, and heart rate, while stroke volume index was increased.

Among 839 patients with NYHA class II-III heart failure treated for 26 to 52 weeks in 4 U.S. placebo-controlled trials, average left ventricular ejection fraction (EF) measured by radionuclide ventriculography increased by 8 EF units (%) in *Coreg* patients and by 2 EF units in placebo patients (between-group difference of 6 EF units). This treatment effect was nominally statistically significant in each trial.

Hypertension

Pharmacodynamics

The mechanism by which β-blockade produces an antihypertensive effect has not been established.

β-adrenoreceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol (1) reduces cardiac output in normal subjects; (2) reduces exercise- and/or isoproterenol-induced tachycardia and (3) reduces reflex orthostatic tachycardia. Significant β-adrenoreceptor blocking effect is usually seen within 1 hour of drug administration.

α_1-adrenoreceptor blocking activity has been demonstrated in human and animal studies, showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes vasodilation and (3) reduces peripheral vascular resistance. These effects contribute to the reduction of blood pressure and usually are seen within 30 minutes of drug administration.

Due to the α_1-receptor blocking activity of carvedilol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (1.8%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when Coreg (carvedilol) is administered with food at the recommended starting dose and titration increments are closely followed (see DOSAGE AND ADMINISTRATION).

In hypertensive patients with normal renal function, therapeutic doses of *Coreg* decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma flow. Changes in excretion of sodium, potassium, uric acid and phosphorus in hypertensive patients with normal renal function were similar after *Coreg* and placebo.

Coreg has little effect on plasma catecholamines, plasma aldosterone or electrolyte levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It also increases levels of atrial natriuretic peptide.

CLINICAL TRIALS

Congestive Heart Failure

Four U.S. multicenter, double-blind, placebo-controlled studies enrolled 1094 patients (696 randomized to carvedilol) with NYHA class II-III heart failure and ejection fraction ≤0.35. The vast majority were on digitalis, diuretics, and an ACE inhibitor at study entry. Patients were assigned to the studies based upon exercise ability. An Australia-New Zealand study also enrolled 415 patients (half randomized to carvedilol) with less severe heart failure. All protocols excluded patients expected to undergo cardiac surgery during the 6 to 12 months of double-blind follow-up. All randomized patients had tolerated a 2-week course on carvedilol 6.25 mg b.i.d.

In each study, there was a primary end-point, either progression of heart failure (one U.S. study) or exercise tolerance (2 U.S. studies meeting enrollment goals and the Australia-New Zealand study). There were many secondary end-points specified in these studies, including NYHA classification, patient and physician global assessments, and cardiovascular hospitalization. Death was not a specified end-point in any study, but it was analyzed in all studies. Other analyses not prospectively planned included the sum of deaths and total or cardiovascular hospitalizations. In situations where the primary end-points of a trial do not show a significant benefit of treatment, assignment of significance values to the other results is complex, and such values need to be interpreted cautiously.

The results of the U.S. and Australia-New Zealand trials were as follows:

Slowing Progression of Heart Failure: One U.S. multicenter study (366 subjects) had as its primary end-point the sum of cardiovascular mortality, cardiovascular hospitalization, and sustained increase in heart failure medications. Heart failure progression was reduced, during an average follow-up of 7 months, by 48% (p=0.008).

In the Australia-New Zealand study, death and total hospitalizations were reduced by about 25% over 18 to 24 months. In the three largest U.S. studies, death and total hospitalizations were reduced by 19%, 39% and 49%, nominally statistically significant in the last two studies. The Australia-New Zealand results were statistically borderline.

Functional Measures: None of the multicenter studies had NYHA classification as a primary end-point, but all such studies had it as a secondary end-point. There was at least a trend toward improvement in NYHA class in all studies. Exercise tolerance was the primary end-point in 3 studies; in none was a statistically significant effect found.

Subjective Measures: Quality of life, as measured with a standard questionnaire (a primary end-point in one study), was unaffected by carvedilol. However, patients' and investigators' global assessments showed significant improvement in most studies.

Mortality: Mortality was not a planned end-point in any study. Overall, in the U.S. trials, mortality was reduced, nominally significantly so in 2 studies, but the actual effect size and statistical significance of this observation are difficult to define.

Hypertension

Coreg was studied in two placebo-controlled trials that utilized twice-daily dosing, at total daily doses of 12.5 to 50 mg. In these and other studies, the starting dose did not exceed 12.5 mg. At 50 mg per day, *Coreg* reduced sitting trough (12-hour) blood pressure by about 9/5.5 mm Hg; at 25 mg/day the effect was about 7.5/3.5 mm Hg. Comparisons of trough to peak blood pressure showed a trough to peak ratio for blood pressure response of about 65%. Heart rate fell by about 7.5 beats per minute at 50 mg/day. In general, as is true for other β-blockers, responses were smaller in black than non-black patients. There were no age- or gender-related differences in response.

The peak antihypertensive effect occurred 1 to 2 hours after a dose. The dose-related blood pressure response was accompanied by a dose-related increase in adverse effects (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

Congestive Heart Failure

Coreg is indicated for the treatment of mild or moderate (NYHA class II or III) heart failure of ischemic or cardiomyopathic origin, in conjunction with digitalis, diuretics, and ACE inhibitor, to reduce the progression of disease as evidenced by cardiovascular death, cardiovascular hospitalization, or the need to adjust other heart failure medications.

Coreg may be used in patients unable to tolerate an ACE inhibitor. *Coreg* may be used in patients who are or are not receiving digitalis, hydralazine or nitrate therapy.

Hypertension

Coreg (carvedilol) is also indicated for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics (see PRECAUTIONS, Drug Interactions).

CONTRAINDICATIONS

Coreg is contraindicated in patients with NYHA class IV decompensated cardiac failure requiring intravenous inotropic therapy, bronchial asthma (two cases of death from status asthmaticus have been reported in patients receiving single doses of *Coreg*) or related bronchospastic conditions, second- or third-degree AV block, sick sinus syndrome (unless a permanent pacemaker is in place), cardiogenic shock or severe bradycardia.

Use of *Coreg* in patients with clinically manifest hepatic impairment is not recommended.

drug.

WARNINGS

Hepatic Injury: Mild hepatocellular injury, challenge, has occurred rarely with *Coreg* trolled studies of hypertensive patients liver function abnormalities reported ences was 1.1% (13 of 1,142 patients) in pa *Coreg* and 0.9% (4 of 462 patients) in tho cebo. One patient receiving carvedilol trolled trial withdrew for abnormal hepati In controlled studies of congestive heart dence of liver function abnormalities repo experiences was 5.0% (38 of 765 patients) ing *Coreg* and 4.6% (20 of 437 patients) placebo. Three patients receiving carvedilol patients receiving placebo (0.5%) in placebo withdrew for abnormal hepatic function. Hepatic injury has been reversible and has short- and/or long-term therapy with minim tomatology. No deaths due to liver function have been reported.

At the first symptom/sign of liver dysfunction dark urine, persistent anorexia, jaundice, rant tenderness or unexplained "flu-like" sy ratory testing should be performed. If the pa ratory evidence of liver injury or jaundice, be stopped and not restarted.

Peripheral Vascular Disease: β-blockers can aggravate symptoms of arterial insufficien with peripheral vascular disease. Caution cised in such individuals.

Anesthesia and Major Surgery: If *Coreg* tre continued perioperatively, particular care sh when anesthetic agents which depress myoc such as ether, cyclopropane and trichloroeth See OVERDOSAGE for information on treat cardia and hypertension.

Diabetes and Hypoglycemia: β-blockers may the manifestations of hypoglycemia, particul dia. Nonselective β-blockers may potentiate hypoglycemia and delay recovery of glucos Patients subject to spontaneous hypoglyce patients receiving insulin or oral hypoglyc should be cautioned about these possibilities should be used with caution. In congestive tients, there is a risk of worsening hyperglyc CAUTIONS).

Thyrotoxicosis: β-adrenergic blockade may signs of hyperthyroidism, such as tachycardia drawal of β-blockade may be followed by an the symptoms of hyperthyroidism or may roid storm.

PRECAUTIONS

General

Since Coreg (carvedilol) has β-blocking a not be discontinued abruptly, particularly ischemic heart disease. Instead, it should b over 1 to 2 weeks.

In clinical trials, *Coreg* caused bradycardia hypertensive patients and 9% of congestive h tients. If pulse rate drops below 55 beats/m should be reduced.

Hypotension and postural hypotension occur syncope in 3.4% of congestive heart failure ing carvedilol compared to 3.6% and 2.5% tients, respectively. The risk for these eve during the first 30 days of dosing, corresponding titration period and was a cause for discon apy in 0.7% of carvedilol patients, compared cebo patients.

Postural hypotension occurred in 1.8% and of hypertensive patients, primarily following or at the time of dose increase and was a tinuation of therapy in 1% of patients.

To decrease the likelihood of syncope or s sion, treatment should be initiated with 3 congestive heart failure patients and 6.25 pertensive patients. Dosage should be slowly, according to recommendations in the ADMINISTRATION section, and the drug with food. During initiation of therapy, be cautioned to avoid situations such as ous tasks, where injury could result shou

Rarely, use of carvedilol in patients with failure has resulted in deterioration of tients at risk appear to be those with (systolic BP<100 mm Hg), ischemic hear fuse vascular disease, and/or underlying Renal function has returned to baseline was stopped. In patients with these risk mended that renal function be monitore tion of carvedilol and the drug discontinu duced if worsening of renal function occ